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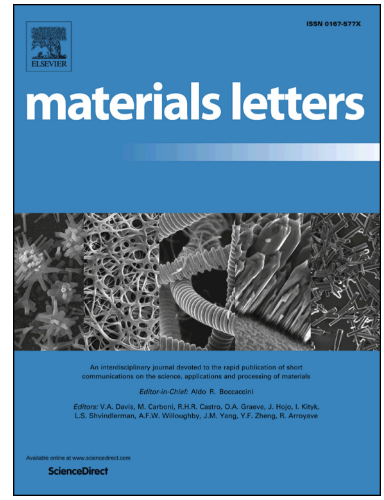

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Manufacturing of biocompatible porous titanium scaffolds using a novel spherical sugar pellet space holder

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Abstract

A new and highly biocompatible space holder material is proposed for manufacturing of porous titanium with open and interconnected pore morphologies through powder metallurgy techniques. Sugar pellets are compacted with titanium powder and then removed by dissolution in water before sintering. The morphology, pore structure and porosity were observed by optical microscopy, SEM and micro-CT. The porous titanium has highly spherical pore shapes, well-controlled pore sizes and high interconnectivity. The results suggest that porous titanium scaffolds generated using this manufacturing route have the potential for hard tissue engineering applications.

Key words

Porous scaffolds; titanium; powder metallurgy; space holder

Introduction

Porous scaffolds, serving as templates that support newly formed bone cells, are a new approach to repair and remodel damaged bone tissue [1,2]. Synthetic materials such as ceramics [3], polymeric materials [4] and metallic alloys [5] offer advantages such as customized geometries and the elimination of potential disease transmission from donor to recipient through autogenous bone grafts [6]. Of all synthetic materials, titanium and its alloys are acknowledged to be amongst the most suitable materials for bone tissue engineering due to an excellent combination of mechanical properties and high biocompatibility [7].

There are various methods to fabricate porous metallic scaffolds including powder sintering, solid-state foaming and rapid prototyping [8]. Powder sintering has been widely used as the material blending and compaction processes allow for customization of material compositions, mechanical properties and shapes in order to produce implants with the desired characteristics. Powder sintering has its advantages over other manufacturing methods. The process is very simple and economical. Powder sintering can be coupled with techniques employing space holders to form pores and can achieve higher levels of porosity and give better control over the porous structure of the scaffolds than other techniques. The space holder particles are mixed with metal powders, then compacted and are removed either before or during sintering. Space holder materials such as sodium chloride [9], carbamide [10], magnesium [11], tapioca [12] and saccharose [13] have been used and can be removed by evaporation or by dissolution.

In this work, a new space holder material is proposed. Pharmaceutical sugar spheres, made of sucrose and starch, are a widely used medication excipient for sustained or extended dosage release. With low friability, consistent sphericity, tight particle size control, high batch-to-batch uniformity and excellent biocompatibility, sugar pellets are an ideal space holder material. The results show that sugar pellets are easily removed from the compacted titanium powders and can generate controlled pore distributions with highly spherical shapes and good interconnectivity.

Materials and Methodology

Titanium hydride-dehydride powder (>99.9% purity) with particle sizes of around 45 µm was used as the base powder due to its excellent sinterability. Spherical sugar pellets, as shown in Figure 1, (supplied by JF-Pharmaland Technology Development Co., Ltd, China) were used as the space holder. The volumetric amount of sugar pellets was of 30, 40, 50, 60 and 70% which correspond to the desired levels of porosity. The sugar pellets and titanium powder were mixed in a 3D turbula mixer for 20 min. The powder mixtures were then uniaxially die pressed at 800 MPa to obtain cylindrical samples of 10 mm in diameter and 10 mm in height. High compaction pressure was employed to prevent sample disintegration during dissolution of the sugar pellets. The space holder was dissolved in distilled water at a temperature of 70-80 °C with constant stirring using a magnetic stirrer. The total dissolution time was 4 hrs with two water changes to ensure proper elimination of the sugar. Samples were then dried in an oven at 90 °C for 2 hrs. Sintering was carried out in a high vacuum furnace at 1300 °C for 2 hrs at a vacuum pressure of 10^{-5} Torr. In order to prevent contamination, all samples were placed on an Al_2O_3 ceramic crucible during sintering. The density of the sintered samples was determined by the Archimedes method. The percentage of open porosity P_{Open} , can be calculated:

$$P_{Open} = \frac{\rho_{HG}(W_{Oil} - W_{Air})}{\rho_{Oil}(W_{Oil} - W_{HG})} \times 100$$

Samples were sectioned and polished for microstructure and pore surface morphology analyses. The porous structure and interconnectivity were evaluated by scanning electron microscopy (SEM) and micro–computed tomography (micro-CT). Mechanical properties of porous titanium scaffold samples were investigated using compression tests. The tests were carried out with Instron 5584 test machine. The specimens were compressed at cross head velocity of 0.5 mm/min at room temperature.

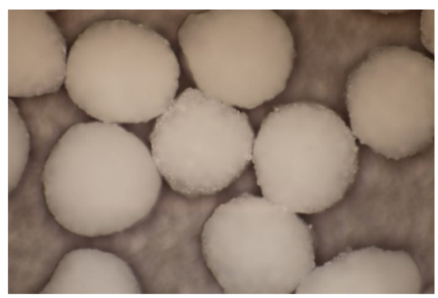
Characteristics	Description	Morphology
Density	1.425 g/cm^3	
Particle sizes	0.212-0.355mm 0.3-0.425mm 0.425-0.5mm	
Chemical	$(C_6H_{10}O_5)_n$, $C_{12}H_{22}O_{11}$	

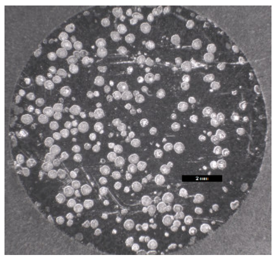
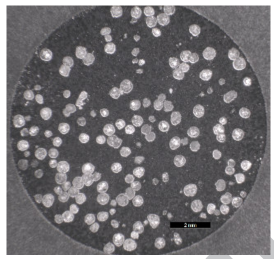
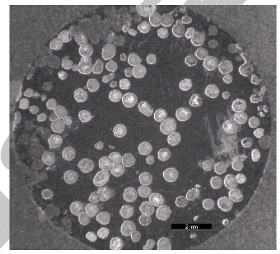
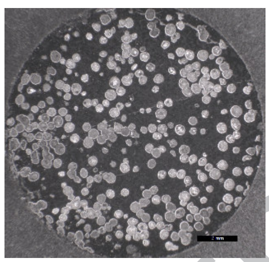
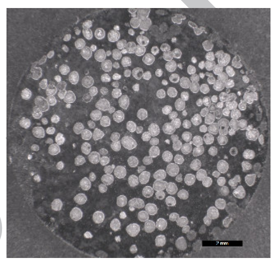
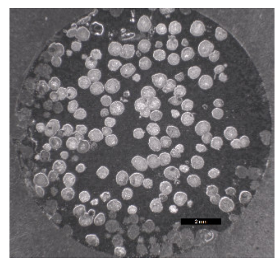
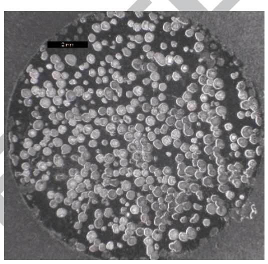
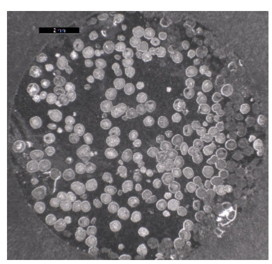
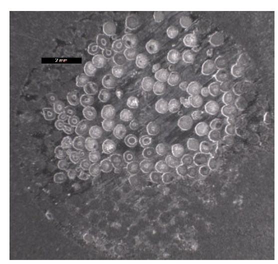
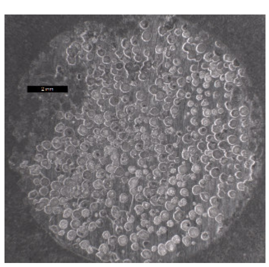
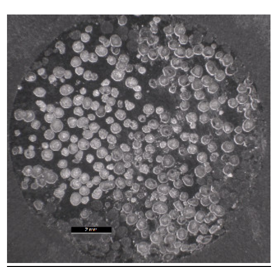
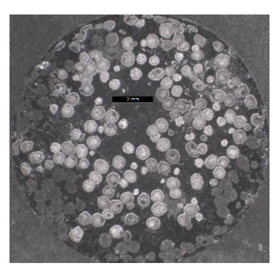
Figure 1. Sugar pellets characteristics

Results and Discussion

The diameter of sugar pellets was chosen according to previous research showing that the optimal size of pores for bone ingrowth is around 400 µm in order to allow formation of complete Haversian units inside the pores [14]. Table 1 shows the measured density and corresponding porosities for different sugar pellet fractions. Density and porosity show uniformity for the different sugar pellet fractions. The measured porosity is around 10% lower than the theoretical value calculated on the basis of the sugar pellet space holder volumes. This difference could be due to shrinkage during sintering as well as a proportion of enclosed pores. The pore interconnectivity can be assessed from the ratio of open porosity to the total porosity. It indicates that it increases with the percentage of sugar pellets. When the designed porosity is up to 70%, open porosity almost reaches the same level of general porosity (up to 98%), which means almost all the pores are interconnected. Figure 2 shows the polished cross-sections of the samples revealing the pore sizes and distributions. For similar volumes of porosity, smaller pellets create more pores, which potentially increase the levels of pore interconnectivity, but larger pellets increase the area of connectivity between the individual pores. Reductions in the thickness of the walls which occur with increasing porosity can affect the mechanical properties of the porous structures [15]. This can be addressed by using smaller pellets as the space holder.

Table 1. Density and porosity of sintered titanium samples

Sugar pellets, (%)	30			40			50			60			70		
Pore size, (μm)	212-355	300-425	425-500	212-355	300-425	425-500	212-355	300-425	425-500	212-355	300-425	425-500	212-355	300-425	425-500
Density, (g/cm^3)	3.57	3.60	3.56	3.35	3.29	3.17	2.99	3.07	3.11	2.55	2.62	2.62	2.16	2.18	2.05
Relative density	0.79	0.80	0.79	0.74	0.73	0.70	0.66	0.68	0.69	0.57	0.58	0.58	0.48	0.48	0.46
General porosity, (%)	20.77	20.11	20.99	25.65	26.99	29.65	33.64	31.87	30.98	43.41	41.86	41.86	52.06	51.62	54.51
Open porosity, (%)	2.15	2.23	2.89	7.92	7.77	10.93	15.89	11.32	15.27	39.41	26.74	30.76	51.08	50.04	52.7
Interconnectivity, (%)	10.35	11.09	13.77	30.88	28.79	36.86	47.24	35.52	49.29	90.79	63.88	73.48	98.12	96.94	96.68

Sugar pellet size, (μm) / Porosity, (%)	212-355	300-425	425-500
30			
40			
50			
60			
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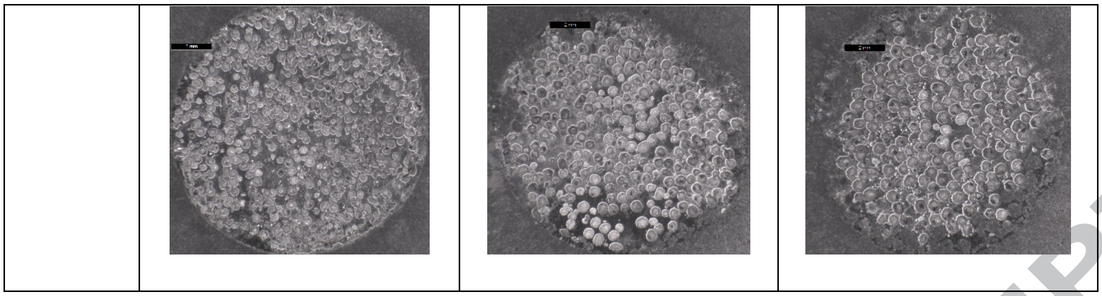
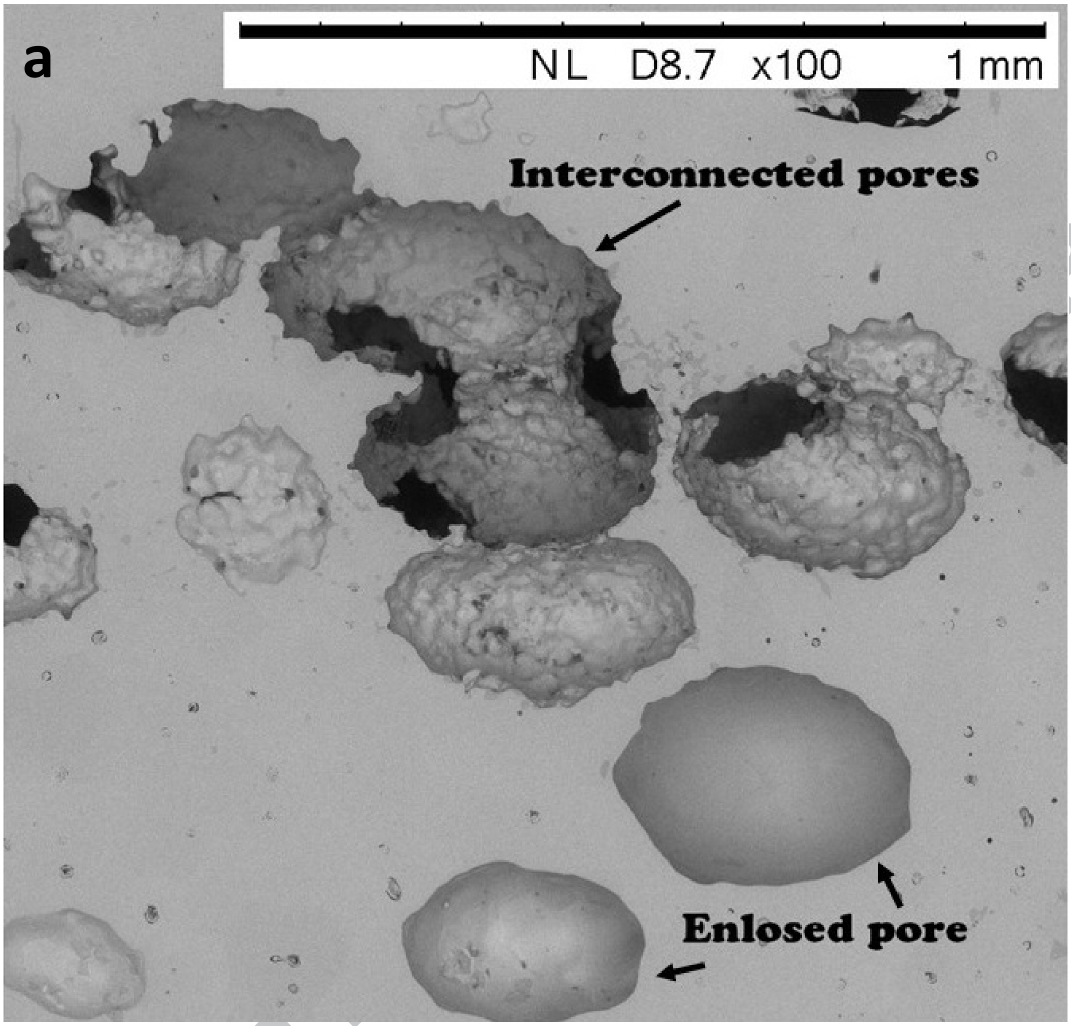


Figure 2. Microscopy of cross sections of titanium foam samples with designed porosities of 30, 40, 50, 60 and 70% with spherical pores of diameter of 0.212-0. 355, 0.3-0.425 and 0.425-0.5mm.

Typical pore structures are shown in Figure 3. The SEM image (Figure 3a) reveals that pore walls are reasonably smooth and spherical with clear grain boundaries evident on the inner pore walls. Most of the pores are connected to other pores. The edge formed by polishing is smooth and sharp, exhibiting greater mechanical integrity when compared to other porous titanium structures reported in literature [9,12,13,16,17]. As compared to those of other space holder materials such as sodium chloride [9], dextrin [16] and saccharose [13], the voids have higher sphericity, are more uniform in shape and are homogenously distributed in the sample with high interconnectivity. Size differences in the pores are due to asymmetrical sectioning of the pores. The small voids (small dark spots on the polished surface of a few microns in diameter) result from the powder compaction and sintering process as fully dense titanium structures are difficult to achieve using the press-and-sinter method [18]. Figure 3b shows the interior structure of the titanium foam. The titanium foam was mechanically cracked and opened for observation. The interconnected-channels between the pores can be clearly observed. The presence of interconnecting pores is essential to prevent blind alleys with low oxygen tension which can prevent the osteoblastic differentiation [19].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Interconnected pores
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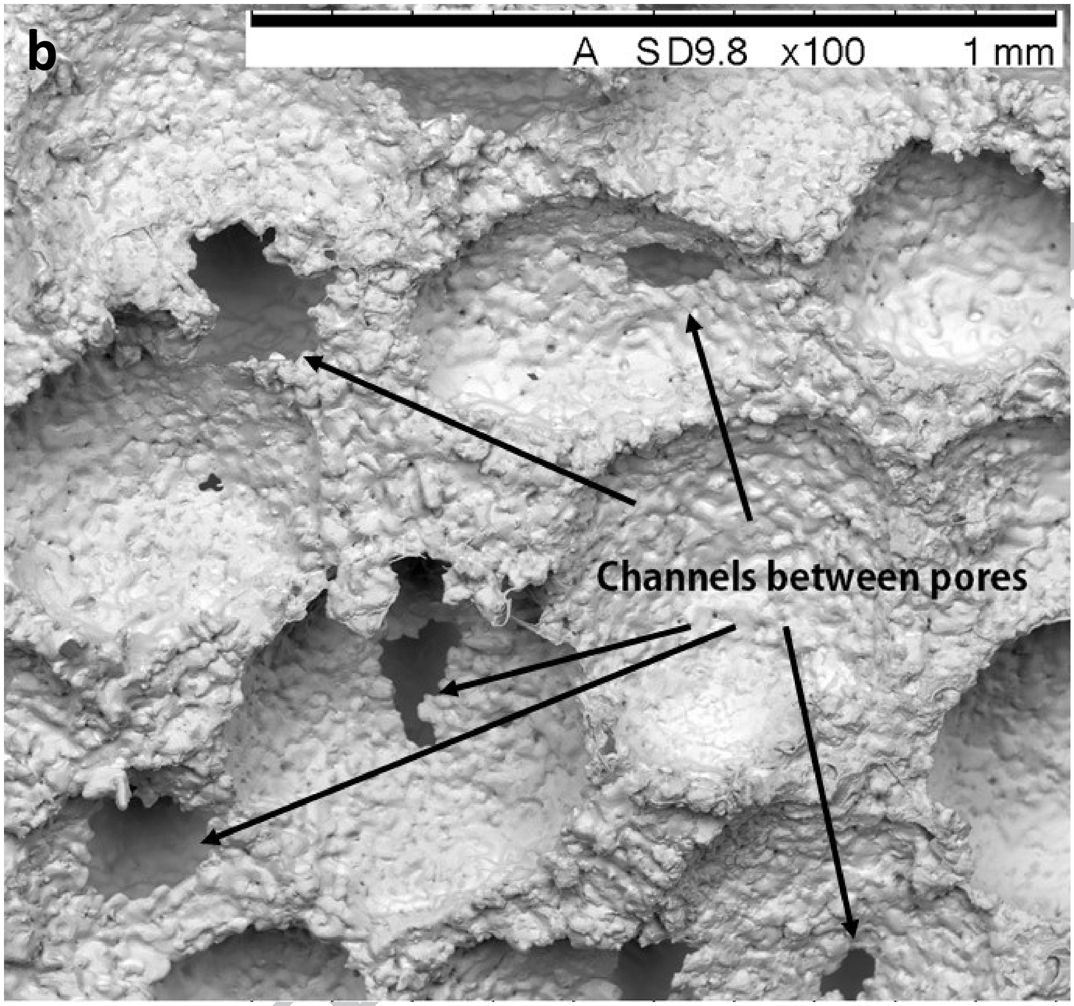

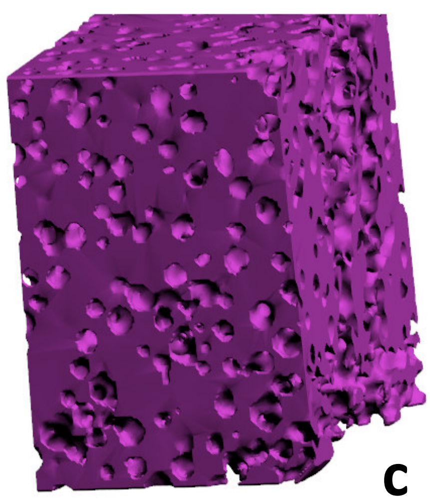
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Figure 3. Pore structures: (a) polished cross-section viewed by scanning electron microscopy (SEM); (b) mechanically cracked open surface viewed by scanning electron microscopy (SEM); (c) Micro-CT measurement

Computed tomography was used to measure not only external and internal shapes but also 2D surface and 3D space parameters such as pore distribution and porosity related to bone histomorphometry. The cross sections of the sample were recorded in three directions with step sizes of 0.01 mm. Mimics® was used to reconstruct the 3 dimensional structure from the hundreds of cross sections. Figure 3(c) corresponds to the centre of a sample designed with 30% porosity using 0.3-0.425mm sugar pellets. The CT analysis showed a high level of correspondence between the designed porosity and the obtained one. Using Mimics®, the porosity was measured to be around 22.5%, which is very close to the results from the Archimedes method. The voids inside the sample are uniformly distributed and are spherical in shape with good interconnectivity. The sugar crystals were totally removed during dissolution in water, giving well-defined pores. The open pores are present from the surface through to the centre which is beneficial for osseointegration. Compression tests were carried out to examine the mechanical properties of the scaffolds. The elastic modulus of the porous scaffold is 18.5, 16.4 and 12.1 GPa, respectively, for 30%, 40% and 50% porosity with pore size of 0.3-0.425 mm. This is consistent with the characteristics of natural bone, which is 0.1-20 GPa[1].

The most comparable space holder to the sugar pellets is saccharose. Jakubowicz et. al. [13] investigated titanium foam fabricated using saccharose as a space holder which was removed by water dissolution before sintering in vacuum (10^{-2} mbar) for 1 h. The main drawback to this method is that it is difficult to control the pore shape and size as the saccharose is in the order of millimeters in diameter and has a natural cubic structure. Spherical saccharose can be made from the original polyhedral ones through milling for 50 h but the shape is hard to control and it can introduce contamination. In our case, the sugar pellets are made from sugar and starch. Both materials are safe in the human body and it is easy to control the shape and size of the pellets. Because of this flexibility, it is possible to manufacture porous structures of different porosity, pore sizes and geometry.

Manufacturing of the metallic scaffold with controlled architecture is possible by additive manufacturing (AM) methods such as selective laser melting (SLM) or selective electron beam melting (SEBM). However, one drawback is the requirement to generate support for the fabricated parts. The second disadvantage is the necessity of post-processing to improve the surface parameters, such as roughness, and to remove the unmelted powder particles.[20] In our study, it is not necessary for post-processing as the structure is as designed after sintering and with satisfying surface roughness.

Conclusion

This work demonstrates the application of powder sintering using spherical pharmaceutical sugar pellets as a space holder material to produce porous titanium scaffolds. Sugar pellets, with well controlled sizes and high biocompatibility are an ideal space holder which are easily remove. Titanium scaffolds with different levels of porosity and varying pore sizes were synthesized and exhibited highly spherical pore shapes with high interconnectivity. The titanium scaffolds produced through this method have excellent potential for use in hard tissue engineering applications.

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Figure Caption

Figure 1. Sugar pellets characteristics

Figure 2. Microscopy of cross sections of titanium foam samples with designed porosities of 30, 40, 50, 60 and 70% with spherical pores of diameter of 0.212-0. 355, 0.3-0.425 and 0.425-0.5mm.

Figure 3. Pore structures: (a) polished cross-section viewed by scanning electron microscopy (SEM); (b) mechanically cracked open surface viewed by scanning electron microscopy (SEM); (c) Micro-CT measurement

Tables

Table 1. Density and porosity of sintered titanium samples

Highlights:

- A novel biocompatible space holder for manufacturing porous scaffold is proposed
- The scaffolds are produced with highly spherical pore shapes from space holder
- The pores manufactured are with well-controlled sizes and high interconnectivity
- The manufacturing route has the potential for hard tissue engineering applications
- Micro-CT is used to evaluate the porous titanium scaffolds

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